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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUSSOW, ANNE	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,445	NORDSTEDT ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11,20-33,37-55,59-63 and 68-70* is/are pending in the application.

4a) Of the above claim(s) *2,3,5,6,42-50,61-63 and 69* is/are withdrawn from consideration.

5)☒ Claim(s) *1,11,20-33,51-55,59,68 and 70* is/are allowed.

6)☒ Claim(s) *9,37,40 and 60* is/are rejected.

7)☒ Claim(s) *4,38,39 and 41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6, 33, 37, and 39 have been amended.

Claims 7, 8, and 64-67 have been canceled.

Claim 70 has been added.

Claims 2, 3, 5, 6, 9, 42-50, 61-63, and 69 remain withdrawn.

2. Claims 1, 4, 11, 20, 21, 28-33, 37-41, 51-66, 59, 60, 68, and 70 are under examination.

3. The following office action contains NEW GROUNDS of Rejection.

4. Applicant has requested rejoinder of Claims 2, 3, 5, 6, 9, and 33. Claims 9 and 33 are hereby rejoined with the claims under examination because upon further consideration they read on the elected antibody and the 6 CDRs under examination. Claims 2, 3, 5, and 6 read on a portion of the elected CDRs, but not on all 6 elected CDRs. Therefore, these claims have not been rejoined for examination.

Objections Withdrawn

5. The objections to claims 37 and 40 as being of improper dependent form are withdrawn in view of applicant's amendment to the claims.

Rejections Withdrawn

6. The rejection of claims 54 and 55 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment to the claims.

7. The rejection of claims 1, 4, 11, 20, 21, 28-32, 38, 39, 41, 51-55, 59, 60 and 68 under 35 U.S.C. 112, first paragraph as lacking enablement for claiming an antibody lacking all 6 CDRs is withdrawn in view of applicant's amendment to the claims.

8. The rejection of claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, and 59 under 35 U.S.C. 101 as being directed to non-statutory subject matter is withdrawn in view of applicant's amendment to the claims.

Objections Maintained

9. The objection to claim 4 is maintained for being dependent upon a withdrawn claim.

10. Claims 38, 39, and 41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Rejections Maintained/ NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The rejection of claims 37 and 40 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

The response filed May 5, 2008 has been carefully considered but is deemed not to be persuasive. The response states that the present specification discloses several antibodies that bind to the C-terminal domain of ApoE. Applicants identified an antibody having the heavy chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 24, 25 and 26, respectively and light chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 33, 34 and 35, respectively, that binds to the C-terminal domain of ApoE. This antibody is referred to in their specification as "807A-M0028-B02" (see Table 8 at page 94, line 2). Applicants also produced affinity matured variants of this antibody, which variants retain the ability to bind to the C-terminal domain of ApoE. The CDR sequences of these affinity matured variants are described in Table 38 at page 144 of their specification and the sequences of selected variants are shown in Tables 43 and 44 at pages 149-150 of their specification.

Applicants' specification also discloses methods that may be used to obtain affinity matured variants (see page 28, line 2, to page 30, line 20) and describes how the affinity matured variants of an antibody having the heavy chain CDR sequences

shown in SEQ ID NOS: 24 to 26 and the light chain CDRs shown in SEQ ID NOS: 33 to 35 were obtained (see Examples 38 and 39 at pages 82-89).

The present specification thus provides sufficient disclosure that would enable the skilled artisan to make and/or use not only an antibody having the CDR sequences of SEQ ID NOS: 24 to 26 and the light chain CDR sequences of SEQ ID NOS: 33 to 35, but also to make and/or use affinity matured variants of these sequences that bind to the C-terminal domain of ApoE and to human plaques (see response page 16).

In response to this argument, while applicant has amended claim 1 to recite an antibody comprising all 6 CDRs - 3 of the heavy chain and 3 of the light chain- and the examiner has withdrawn the enablement rejection for this claim and subsequent dependent claims. Claims 37 and 40 recite an antibody comprising the CDR regions of only the heavy chain or the light chain, thus only 3 CDRs. The specification does not disclose an antibody that comprises fewer than 6 CDRs. As set forth in the previous office action, the state of the art is such that an antibody comprising fewer than all 6 CDRs would not be predicted to bind to antigen.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

13. The rejection of claim 60 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

The response filed May 5, 2008 has been carefully considered but is deemed not to be persuasive. The response states that Huang et al teach that C-terminal truncated

forms of ApoE are present to a greater extent in brains of subjects affected by Alzheimer's disease than in normal brains. The present specification demonstrates that the C-terminal truncated forms of ApoE are present in plaques. Therefore, the antibodies of the claimed invention bind to ApoE in plaques. The bound antibodies would facilitate the destruction of the plaques as the plaques become coated with antibody, which will trigger direct destruction of the plaques by immune mechanisms such as complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC). For example, the antibody-coated plaques can be removed by phagocytosis, such as by internalization by microglia (see page 49, line 30, to page 50, line 19, of the specification).

Applicants' specification demonstrates that the antibodies that bind to ApoE-CTD were able to stimulate phagocytic uptake of CTD-bearing beads by human macrophage/ microglia-like cells in a concentration-dependent fashion (see Example 32 at pages 78-79). Therefore, the present specification provides evidence that antibody binding to ApoE-CTD in amyloid plaques would facilitate removal of the plaques (see response pages 17-18)

In response to this argument, the example pointed to by the applicant on pages 49-50 of the specification is a generic hypothetical example and working example 32 on pages 78-79 of the specification describes an in vitro binding and phagocytotic assay. The examples do not provide evidence to support treatment of disease with the instantly claimed antibody. The specification does not disclose whether the binding of the antibody *in vivo* results in removal of existing plaques or inhibition of the formation of

new plaques. The specification does not disclose other amyloid disorders or models of other amyloid disorders.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

14. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim recites an antibody or antibody fragment according to claim 1, wherein said polypeptide having the amino acid sequence of a part of SEQ ID NO: 1 comprises the sequence shown in SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19.

The specification discloses production of antibodies that specifically bind to the protein of SEQ ID No. 1. The specification does not disclose antibodies that bind to the peptides of SEQ ID Nos. 2, 5, 7, 9, 10, 12-19.

Although the specification teaches that variants can be readily screened, the specification and the claim do not provide any guidance on the structure of the polypeptide and what changes can or can not be made. For example, Lederman, et al. (Molecular Immunology, 1991. Vol. 28, pages 1171-1181) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see

entire document). Li et al (Proceedings of the National Academy of Sciences, 1980. Vol. 77, pages 3211-3214) disclose dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Further, Kokolus, et al. teach that a randomly selected oligopeptide from within a larger polypeptide molecule only rarely elicits a high titer, high affinity antibody response that reacts with the native molecule (column 4, lines 7-11). Thus, an antibody which binds to a polypeptide would not necessarily bind to the native protein and visa versa.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce an antibody to a peptide that would bind the same structure as an antibody to a complete protein. The specification does not teach antibodies to the specific peptides of claim 9.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to produce the claimed antibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the antibody which binds both the specific peptides and the specific full length protein, commensurate in scope with the claimed invention.

Conclusion

15. Claims 1, 11, 20, 21, 28-33, 51-55, 59, 68, and 70 appear to be in condition for allowance.

Claims 9, 37, 40, and 60 are rejected.

Claims 4, 38, 39, and 41 are objected.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

July 30, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643